

Letters to the Editor

Tacrolimus ointment reduces staphylococcal colonization of atopic dermatitis lesions

To the Editor:

Skin colonization by *Staphylococcus aureus* affects approximately 90% of patients with atopic dermatitis (AD), with *S aureus* skin infections being a common complication of AD.¹ Treatment with potent topical corticosteroids reduces *S aureus* colonization. Improvement of the skin's barrier function and a decrease in the adhesiveness of *S aureus* to corneocytes are considered to contribute to this effect.²

Tacrolimus ointment is a promising novel treatment for AD^{3,4} that seems to work by local inhibition of T-cell activation and inhibition of the expression of inflammatory cytokines and the high-affinity IgE receptor on antigen-presenting Langerhans' cells.⁵ Given the importance of skin infection in AD, we investigated *S aureus* skin colonization in patients treated twice daily for up to 1 year with 0.1% tacrolimus ointment. This single-center study was conducted in the context of a multicenter, noncomparative, long-term safety study in adult patients with moderate-to-severe AD.⁴ At our center, 19 patients (4 male, 15 female) completed 6 months of therapy, and 9 (1 male, 8 female) completed 12 months (the multicenter study included 6-month and 12-month study populations). Assessments were at baseline, weeks 1 and 2, and monthly thereafter. Agar plate lifts, from the worst lesion of each patient, were obtained by applying a contact plate (NUNC, Roskilde, Denmark) for 5 seconds. Cultures were incubated aerobically in a cystine, lactose, electrolyte-deficient agar medium at 35°C for 24 hours. The following criteria were used to identify *S aureus*: typical colony morphology on the contact plates and in pure cultures on a blood agar plate and a positive catalase test result and positive DNase test result or a positive coagulase tube test result. The density of *S aureus* colonies was expressed as colony-forming units per square centimeter (CFU/cm²). For the eczema score, erythema, induration, excoriation, lichenification, and scaling were each graded on a scale of 0 to 3 and summed (maximum 15). Changes in CFU/cm² and in the eczema score were calculated from baseline to week 1, month 6, and month 12 for each patient, with statistical comparisons being carried out with the Wilcoxon signed rank test.

By the first week of treatment, *S aureus* colonization and the eczema score markedly decreased (Fig 1). The median decrease in CFU/cm² was 59.1 at week 1 compared with baseline ($P = .012$, $n = 19$), 102.4 at month 6 ($P < .001$, $n = 19$), and 234.9 at month 12 ($P = .008$, $n = 9$). The median decrease in the eczema score was 4.5 at week 1 compared with baseline ($P < .001$, $n = 15$), 5.5 at month 6 ($P < .001$, $n = 15$), and 8.0 at month 12 ($P = .008$, $n = 8$).

The healing of skin lesions, as demonstrated by the improvement in the eczema score and improvement in skin-barrier function, probably contributed to the decrease in staphylococcal colonization. Tacrolimus has no inhibitory effect on bacteria, including *S aureus*.⁶ The reduction in *S aureus* colonization suggests that the local activity of tacrolimus in the skin is not immunosuppressive but immunomodulatory. Clinical studies to date have shown no evidence of an increased risk of bacterial or viral skin infections with tacrolimus ointment.^{3,4}

Only short-term studies have assessed *S aureus* colonization with topical corticosteroids; thus it is impossible to know whether this effect would be maintained with long-term treatment as demonstrated here with tacrolimus ointment. In future assessments of tacrolimus ointment and *S aureus* colonization, it will be important to perform comparative studies with topical corticosteroids.

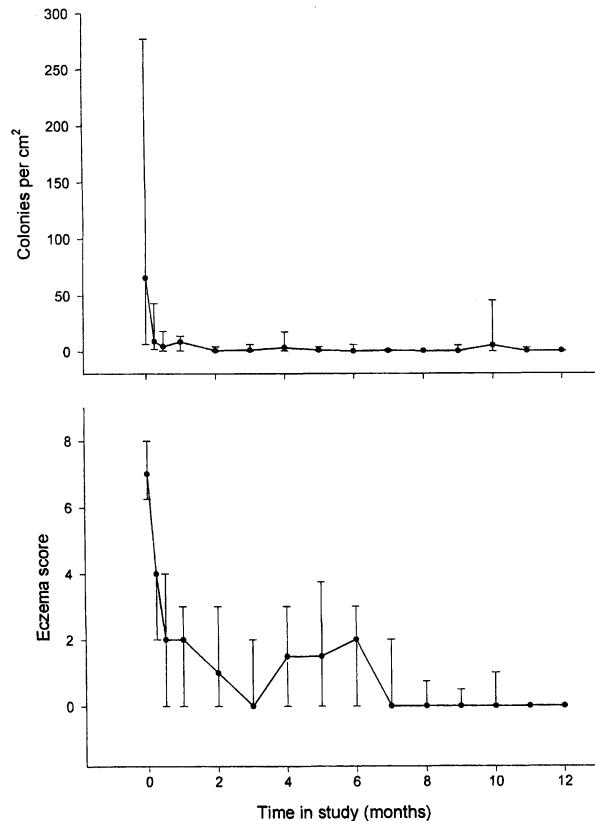


FIG 1. Median (with error bars showing the upper and lower quartiles) *S aureus* CFU/cm² and eczema score in patients who received 0.1% tacrolimus ointment for up to 12 months. Median decreases from baseline to week 1 ($n = 19$), month 6 ($n = 19$), and month 12 ($n = 9$ for CFU/cm²; $n = 10$ for eczema score) were statistically significant for both assessments ($P = .01$, Wilcoxon signed rank test).

S aureus, by release of superantigens, is believed to play an etiologic role in AD,⁷ and superinfection is a common and serious complication of AD. Thus reduction of this trigger has the potential of imparting long-term benefit to patients.

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REFERENCES

1. Aly R. Bacteriology of atopic dermatitis. *Acta Derm Venereol* 1980;92:16-8.
2. Stalder JF, Fleury M, Sourisse M, Rostin M, Pheline F, Litoux P. Local steroid therapy and bacterial skin flora in atopic dermatitis. *Br J Dermatol* 1994;131:536-40.

3. Ruzicka T, Bieber T, Schöpf E, Rubins A, Dobozy A, Bos JD, et al. A short-term trial of tacrolimus (FK506) ointment for atopic dermatitis. *N Engl J Med* 1997;337:816-21.
4. Reitamo S, Wollenberg A, Schöpf E, Perrot JL, Marks R, Ruzicka T, et al. Safety and efficacy of 1 year of tacrolimus ointment in adults with atopic dermatitis. *Arch Dermatol* 2000;136:999-1006.
5. Ruzicka T, Reitamo S, Bieber T. Tacrolimus ointment for atopic dermatitis [letter]. *N Engl J Med* 1998;339:1788-9.
6. Kino T, Hatanaka H, Hashimoto M, Nishiyama M, Goto T, Okuhara M, et al. FK-506, a novel immunosuppressant isolated from a streptomyces. I. Fermentation, isolation, and physico-chemical and biological characteristics. *J Antibiot (Tokyo)* 1987;40:1249-55.
7. Leung DYM. Atopic dermatitis: new insights and opportunities for therapeutic intervention. *J Allergy Clin Immunol* 2000;105:860-76.

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Perennial rhinitis induced by benzoate intolerance

To the Editor:

The role of food additives in allergic diseases is still unclear. Although many studies claiming that food additives may be responsible for a number of clinical conditions including chronic urticaria, angioedema, anaphylaxis, and asthma have been published,¹ most of them were not carried out with stringent criteria, and their results are therefore unproven or not reproducible.^{1,2} Now it is generally accepted that only well-designed studies (ie, double blind, placebo-controlled studies using multiple and randomized placebos) can avoid bias and lead to reliable conclusions. A case of chronic rhinitis caused by intolerance to sodium benzoate diagnosed by rigorously controlled methods is reported here.

A 33-year-old woman came to our allergy department with a 7-year history of perennial rhinitis, characterized by watery rhinorrhea, itching of the nasal mucosa, and frequent episodes of sneezing paroxysms. Antihistamines as well as local corticosteroids had little effect. The patient did not smoke and was otherwise well; she had never had asthma episodes. Several ear, nose, and throat investigations found only scarce inflammatory changes and excluded both structural deformities and polyps. Findings of plain radiographs as well as a coronal CT scan were normal. Blood counts did not show any abnormality.

Results of skin prick tests with commercial extracts of the main seasonal and perennial airborne allergens, including grass, pellitory, mugwort, ragweed, olive, birch, hazel, cypress, house dust mite, several molds, and several animal danders (Allergopharma, Reinbeck, Germany) were negative. In view of the well-known association between additive intolerance and respiratory symptoms such as asthma,^{1,2} an elimination diet (free of food additives) was tentatively started. On the fifth day of this regimen, nasal symptoms totally disappeared. After 1 month of an additive-free diet, during which the woman remained free of symptoms, an open challenge (unrestricted diet for 3 weeks) was carried out. After 3 days nasal symptoms relapsed and worsened progressively, lasting throughout the whole open-challenge period. The additive-free diet was resumed and, again, symptoms gradually disappeared after 4 to 5 days. After 3 weeks without symptoms, the patient underwent double-blind, placebo-controlled peroral challenges with food additives. The substances and doses given are shown in Table I. The patient continued the additive-free diet throughout the study period. Single additives and multiple placebos were challenged 1 week apart in a randomized sequence. Both active substances and placebos were given in identical opaque capsules. The patient was monitored at the allergy center for at least 2 hours after each challenge. Informed, written consent was obtained before the start of the procedure.

About 1 hour after the administration of 50 mg sodium benzoate, the patient reported itching of the nasal mucosa that worsened dur-

TABLE I. Food additives used in challenge tests

Additive	Dose (mg)
Sodium metabisulfite	25
Sodium benzoate	50
Sodium glutamate	100
Sodium nitrate	10
Tartrazine	10
Erythrosine	10
Sorbic acid	100
Butylated hydroxyanisole	10
Talc (placebo)	—

ing the next hour along with the appearance of sneezing and rhinorrhea. Rhinitis lasted for about 36 hours. No other substance induced nasal symptoms. To confirm this finding, we rechallenged the patient 2 weeks later with sodium benzoate and 3 placebos in a double-blind fashion in a randomized sequence. Again, the patient responded to the active substance only; rhinitis lasted about 36 hours. Sodium benzoate intolerance was diagnosed. The patient's prior, unrestricted diet frequently included soft cheeses and wine, which sometimes contain sodium benzoate.

Benzoates are widely used as antimycotic and antibacterial preservatives in foods and beverages. Some uncontrolled or poorly designed studies have reported that sodium benzoate is a possible cause of asthma,³⁻⁶ but this is probably the first report of perennial rhinitis as the only clinical expression of benzoate intolerance. Bias should have been avoided by the diagnostic procedure adopted here. Challenge with sodium benzoate exactly reproduced the clinical symptoms present during the previous 7 years. As in most cases of food additive intolerance, pathogenic mechanisms remain elusive. The observation that perennial rhinitis may be caused by the frequent (probably daily) ingestion of small doses of a nontolerated substance is intriguing and suggests that at least some patients with "chronic vasomotor rhinitis" might in effect be intolerant of a particular food additive.

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REFERENCES

1. Simon RA, Stevenson DD. Adverse reactions to food and drug additives. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW, editors. *Allergy. Principle and practice*. 4th ed. St Louis: Mosby; 1993. p. 1687-704.
2. Bush RK, Taylor SL. Adverse reactions to food and drug additives. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW, editors. *Allergy. Principle and practice*. 5th ed. St Louis: Mosby; 1998. p. 1183-98.
3. Freedman BJ. Asthma induced by sulphur dioxide, benzoate, and tartrazine contained in orange drinks. *Clin Allergy* 1977;7:407-15.
4. Samter M, Beers RF. Intolerance to aspirin: clinical studies and considerations of its pathogenesis. *Ann Intern Med* 1968;68:975-83.
5. Rosenhall L. Evaluation of intolerance to analgesics, preservatives, and food colorants with challenge tests. *Eur J Respir Dis* 1982;63:410-9.
6. Tarlo SM, Broder I. Tartrazine and benzoate challenge and dietary avoidance in chronic asthma. *Clin Allergy* 1982;12:303-12.

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